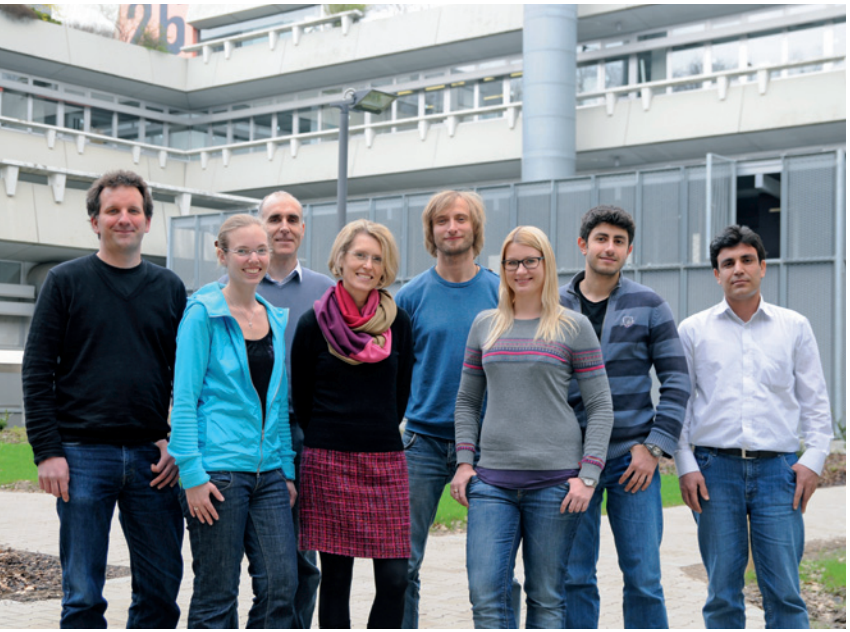


The Team:
Head of Institute: C. Kubisch
Professor: H. Kehrer-Sawatzki
Group Leader/Postdoc: G. Borck
PhD Students: N. Kakar, N. Sowada, J. Vogt, R. Yilmaz
Additional Members of Thesis Advisory Committees:
H.J. Fehling (Ulm), L. Kluwe (Hamburg),
J. Weishaupt (Ulm), B. Wollnik (Köln)

Institute of Human Genetics

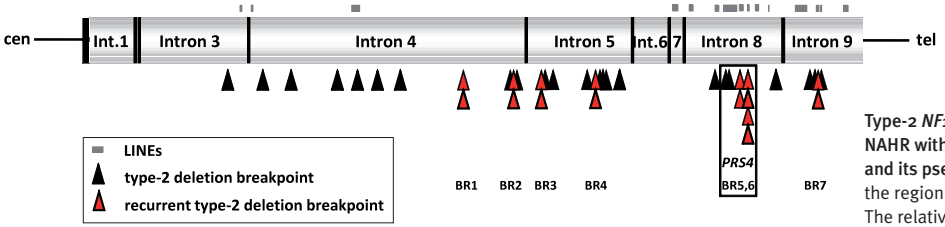
Characterization of Molecular Mechanisms Underlying Human Genetic Diseases

Head: Christian Kubisch

The Institute of Human Genetics offers genetic counseling as well as molecular and cytogenetic diagnostics. Additionally, basic research on various inherited human disorders is performed by different research groups.

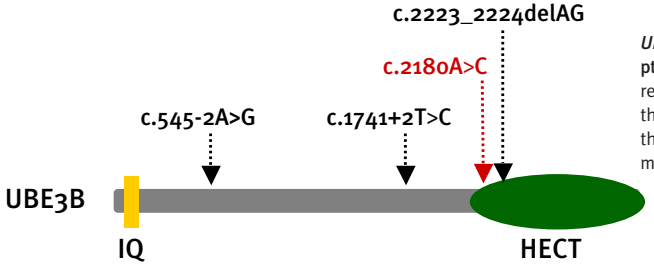
Several aspects of the hereditary cancer syndrome Neurofibromatosis type-1 are investigated by the working group of Prof. Dr. biol. hum. H. Kehrer-Sawatzki. As a member of this group, M. sc. Julia Vogt investigated in her PhD thesis the mutational mechanisms underlying large *NF1* microdeletions which are observed in 5% of all patients with NF1. Four types of *NF1* microdeletions (type-1, type-2, type-3 and atypical) were identified which differ with respect to the extent of the deleted region, the location of the respective breakpoints and the underlying mechanisms. Julia Vogt's work revealed that *NF1* microdeletions with recurrent breakpoints are mediated by nonallelic homologous recombination (NAHR), whereas atypcial *NF1* deletions do not exhibit recurrent breakpoints and are mostly caused by non-homologous end joining and microhomology-mediated replication-dependent recombination. In the course of her PhD thesis, Julia Vogt developed different techniques, including customized Multiplex Ligation-dependent Probe Amplification (MLPA), as well as customized array techniques to improve the identification of *NF1* microdeletion breakpoints at high resolution. By means of these approaches, she found that not only the breakpoints of *NF1* microdeletions mediated by meiotic NAHR but also those mediated by mitotic NAHR cause somatic mosaicism with normal cells in the affected patients cluster within specific regions and encompass only a few kilo-base pairs (Fig.1). Some of these preferred regions of recurrent genomic breakage are located within the *SUZ12* gene and its pseudogene *SUZ12P*. A combination of open chromatin conformation and short non-B DNA-forming repeats is likely to predispose to recurrent mitotic NAHR mediating *NF1* microdeletions with breakpoints located within the *SUZ12* sequences (PhD project, Julia Voigt).

The research group led by Prof. Dr. med. Christian Kubisch focuses on the identification and characterization of novel disease genes underlying monogenic and complex genetic disorders such as hearing impairment, neurodegenerative diseases, migraine, progeroid syndromes and syndromes



Type-2 *NF1* microdeletions are mediated by mitotic NAHR with breakpoints located in the *SUZ12* gene and its pseudogene *SUZ12P*. Exon-intron structure of the region of homology between *SUZ12* and *SUZ12P*. The relative positions of the 40 type-2 *NF1* deletion breakpoint regions are indicated by black triangles. Recurrent breakpoint regions (BR1-BR7) are denoted by red triangles. The rectangular box highlights the NAHR hotspot PRS4, which is located within intron 8.

associated with congenital malformations and intellectual disability. The group recently described a novel human genetic syndrome characterized by facial dysmorphic features, intellectual disability, short stature, microcephaly and low cholesterol levels (blepharophimosis-ptosis-intellectual disability syndrome). This syndrome is caused by biallelic mutations of the *UBE3B* gene which encodes an E3 ubiquitin ligase of unknown function. Ubiquitin ligases transfer ubiquitin on target proteins which will consequently be degraded by the proteasome. The PhD project of MSc Rüstem Yilmaz aims at a functional characterization of UBE3B missense mutations located in the HECT domain of the protein. We will generate constructs containing the *UBE3B* wild-type sequence and several mutations identified in our lab and in others, and will test the ubiquitination capacity of the mutants in in vitro assays. We will also characterize the brains of *Ube3b*$^{-/-}$ mice with respect to histological brain anomalies, anomalies of the morphology and number of synapses, and distribution of synaptic marker proteins. Finally, we will investigate patients with features of the blepharophimosis-ptosis-intellectual disability syndrome but no *UBE3B* mutation in order to identify novel genes implicated in syndromic forms of intellectual disability (PhD project, Rüstem Yilmaz).



***UBE3B* mutations identified in a blepharophimosis-ptosis-intellectual disability syndrome.** Schematic representation of UBE3B with the N-terminal IQ and the C-terminal HECT domain and the positions of three truncating mutations (black) and one missense mutation (red; p.Gln727Pro).

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Selected Publications:

- *Kehrer-Sawatzki H, Vogt J, Mußotter T, Kluwe L, Cooper DN, Mautner VF (2012): Dissecting the clinical phenotype associated with mosaic type-2 NF1 microdeletions. Neurogenetics 13:229-236.*
- *Vogt J, Mussotter T, Bengesser K, Claes K, Högel J, Chuzhanova N, Fu C, van den Ende J, Mautner VF, Cooper DN, Messiaen L, Kehrer-Sawatzki H (2012): Identification of recurrent type-2 NF1 microdeletions reveals a mitotic nonallelic homologous recombination hotspot underlying a human genomic disorder. Hum Mutat 33:1599-1609.*
- *Roehl AC, Mussotter T, Cooper DN, Kluwe L, Wimmer K, Högel J, Zetzmann M, Vogt J, Mautner VF, Kehrer-Sawatzki H (2012): Tissue-specific differences in the proportion of mosaic large NF1 deletions are suggestive of a selective growth advantage of hematopoietic del(+/-) stem cells. Hum Mutat 33:541-550.*
- *Szakszon K, Salpietro C, Kakar N, Knegt AC, Oláh E, Dallapiccola B, Borck G (2013): De novo mutations of the gene encoding the histone acetyltransferase KAT6B in two patients with Say-Barber-Biesecker/Young-Simpson syndrome. American Journal of Medical Genetics A 161:884-888.*
- *Basel-Vanagaite L, Dallapiccola B, Ramirez-Solis R, Segref A, Thiele H, Edwards A, Arends MJ, Miró X, White JK, Désir J, Abramowicz M, Dentici ML, Lepri F, Hofmann K, Har-Zahav A, Ryder E, Karp NA, Estabel J, Gerdin AKB, Podrini C, Ingham NJ, Altmüller J, Nürnberg G, Frommolt P, Abdelhak S, Pasmanik-Chor M, Konen O, Kelley RI, Shohat M, Nürnberg P, Flint J, Steel KP, Hoppe T, Kubisch C, Adams DJ, Borck G (2012): Deficiency for the ubiquitin ligase UBE3B in a blepharophimosis-ptosis-intellectual disability syndrome. American Journal of Human Genetics 91:998-1010.*
- *Borck G, Shin B-S, Stiller B, Mimouni-Bloch A, Thiele H, Kim J-R, Thakur M, Skinner C, Aschenbach L, Smirin-Yosef P, Har-Zahav A, Nürnberg G, Altmüller J, Frommolt P, Hofmann K, Konen O, Nürnberg P, Munnich A, Schwartz CE, Gothelf D, Colleaux L, Dever TE, Kubisch C, Basel-Vanagaite L (2012): eIF2γ mutation that disrupts eIF2 complex integrity links intellectual disability to impaired translation initiation. Molecular Cell 48:641-646.*